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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,322	CURIEL ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 12/12/03 has been entered.

Amended claims 1, 3-7 and 9-12 are pending in the present application, and they are examined on the merits herein.

Response to Amendments

The rejections under 35 U.S.C. 102(b) as being anticipated by Sosnowski et al. (WO 98/40508) or Sosnowski et al. (U.S. Patent 6,613,563) are withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 7 and 9-12 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action mailed on 11/05/03 (pages 3-7).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the claims are drawn to a method of gene delivery by adenoviral vector comprising the step of contacting target cells with an adenoviral vector comprising a targeting component that targets said vector to specific target cells and a tissue-specific promoter that drives the expression of a transgene carried by said vector in said target cells, wherein said adenoviral vector has increased targeting specificity to said targeting cells and results in reduced transgene expression in non-target cells, and wherein the targeting component of said adenoviral vector is a bi-specific molecule that binds to the knob protein of said adenoviral vector and a molecule expressed on said target cells.

The specification teaches by exemplification the preparation of a recombinant AdfltLuc whose luciferase gene expression is operably linked to the endothelial specific promoter flt-1, and the pulmonary endothelial targeting conjugate Fab-9B9 (a conjugate of the Fab fragment of an anti-Ad5 knob antibody 1D6.14 to the mAb 9B9 specific for angiotensin converting enzyme). Applicants further demonstrate that a conjugate-based approach to target pulmonary endothelium *in vivo* via binding to angiotensin converting enzyme in combination with the usage of flt-1 promoter results in a high degree of activity in and specificity for endothelial cells (see example 5 and Figs. 3-5).

When read in light of the specification, the sole purpose for a method of gene delivery by adenoviral vector as claimed is to obtain therapeutic effects *in vivo*, particularly for treating pulmonary vascular diseases (see Summary of the Invention on pages 6-9). The instant disclosure does not teach any other uses for the gene delivery method as claimed. It should be noted that enablement requires the specification to teach how to make and **use** the claimed invention.

(1) The breadth of the claims.

With respect to the elected invention, the instant broad claims encompass a method of gene delivery by adenoviral vector comprising the step of contacting target cells by any route of administration with an adenoviral vector comprising a targeting component which is a bi-specific molecule that binds to the knob protein of the adenoviral vector and a molecule expressed on the target cells, and a tissue-specific promoter that drives the expression of any transgene to attain therapeutic results contemplated by Applicants.

(2) The state and the unpredictability of the art.

The nature of the instant claims falls within the realm of *in vivo* gene therapy. The specification is not enabled for the instant invention because at about the effective filing date of the present application, gene therapy was an immature and highly unpredictable art, particularly for the attainment of any therapeutic effects. This is supported by numerous reviews in the art. For example, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) state "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular

targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first paragraph). At about the effective filing date of the present application (2/14/2001), Romano et al. (Stem Cells 18:19-39, 2000) note that "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned...., despite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame" (see the abstract). It has been recognized that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells. With respect to gene therapy specific for pulmonary diseases, West et al. (Chest 119:613-617, 2001) also note several important barriers that will need to be overcome, including the host inflammatory response, promoter down-regulation, tissue-specific targeting and physical barriers to gene delivery in the airway. West et al. further state "Demonstration of successful gene delivery and transcription has been quite variable in human trials. In general, the level of expression of transgene appears to be quite low. In summary, although there is a great promise for gene therapy in the lung, significant challenges remain in translating this technology to successful human therapy" (see abstract). More recently, Griesenbach et al. (Gene therapy 9:1344-1350, 2002) noted that cystic fibrosis gene transfer efficiency was still low, and most likely insufficient to achieve clinical effect (see abstract).

Thus, it is clear that the attainment of any therapeutic effect through the gene therapy approach was highly unpredictable at the effective filing date of the present application.

(3) The amount of direction or guidance presented.

The instant specification is not enabled for the presently claimed invention. Apart from the exemplification showing the qualitative assessment of luciferase activity or carcinoembryonic antigen gene expression being enhanced in the pulmonary endothelium via a systemic delivery of the AdfltLuc-1D6.14/9B9 complex or AdfltCEA-1D6.14/9B9 complex, respectively in rats, the present disclosure fails to provide any evidence indicating that any therapeutic effect has been achieved *in vivo*, particularly in light of the unpredictable attainment of therapeutic effects via gene therapy known in the art. The specification fails to provide any relevant *in vivo* example (part of guidance) demonstrating that a therapeutic effect has been obtained, particularly for a pulmonary vascular disease, using the modified adenoviral vector system disclosed in the present application. Despite an enhanced detection of luciferase activity and expression of carcinoembryonic antigen in pulmonary endothelium, it is noted that significant expression levels of luciferase were still detected in liver, spleen, muscle, testis, brain and heart tissues of the treated rats (see Figs. 3-5). Furthermore, Sato et al. (Biochem. Biophys. Res. Commun. 244:455-462, 1998) have noted that the use of any tissue-specific promoters for specific cancer gene therapy has been limited because the expression level of these promoters is generally low and may not be sufficient for effective gene therapy (page 455, col. 2, last sentence of first paragraph). Therefore,

given the lack of sufficient guidance provided by the instant specification for a skilled artisan on how to overcome factors known to limit the effectiveness of gene therapy, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Accordingly, due to the lack of sufficient guidance and examples provided by the instant specification regarding to the issues set forth above, the unpredictable nature of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the method as claimed.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 12/12/03 (pages 8-11) have been fully considered, but they are not found persuasive.

Applicants argue basically that the claims are simply drawn to a method of delivering gene to target tissue by the adenoviral vector of the present invention, and that the claims neither recite a method of gene therapy nor a method of obtaining therapeutic effects *in vivo*. Applicants further argue that in view of the detailed description and data presented in the specification, one of ordinary skill in the art can readily practice the instant invention of delivering a gene of interest to a target tissue without undue experimentation.

Applicants' arguments are respectfully found unpersuasive because the sole purpose for a method of gene delivery by the adenoviral vector as claimed is to obtain therapeutic effects *in vivo*, particularly for treating pulmonary vascular diseases (see

Summary of the Invention on pages 6-9; pages 13-14, page 2, lines 4-7). The instant disclosure does not teach any other uses for the gene delivery method as claimed. What is the use for a method of simply delivering a transgene to target cells using the adenoviral vector of the present invention. It should be noted that enablement requires the specification to teach how to make and **use** the claimed invention. As such, upon analysis of the Wands factors as discussed above, it would have required undue experimentation for a skilled artisan to make and **use** the method as claimed to attain any therapeutic effects contemplated by Applicants.

Accordingly, amended claims 7 and 9-12 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1 and 3-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. (WO 98/40508) in view of Muzykantov et al. (Am. J. Physiol. 270: L704-L713, 1996; IDS) for the same reasons already set forth in the previous Office Action mailed on 11/05/03 (pages 11-14).

Sosnowski et al. disclose a tropism-modified adenoviral vector system that specifically target cells (page 4, lines 17-25) comprising: (i) an antibody or fragment thereof that binds an adenoviral capsid protein (e.g., an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), (ii) a targeting ligand that bind to the specifically target cells (including a ligand is an antibody or a fragment thereof, and that the ligand is conjugated to an antibody or fragment thereof that binds an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), and (iii) an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter, including a tissue-specific promoter such as the endothelial-specific VEGF-receptor promoter (elected species, page 75, line 17 continues to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a

molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Sosnowski et al. do not teach specifically the utilization of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system.

However, at the effective filing date of the present application Muzykantov et al. already disclose that the Mab 9B9 to angiotensin converting enzyme is a safe and specific carrier for drug targeting to the pulmonary endothelium, and that it is internalized by endothelial cells both *in vitro* and *in vivo* without significant intracellular degradation (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the tropism-modified adenoviral vector system of Sosnowski et al. by utilizing a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, and more specifically the bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody to target the modified adenoviral vector specifically to pulmonary endothelium in light of the teachings of Muzykantov.

An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a safe and specific carrier for drug targeting to the pulmonary endothelium and that the antibody is

internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells.

One would have a reasonable expectation of success to carry out the presently claimed invention in light of the teachings of Sosnowski et al. and Muzykantov et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 12/12/03 (pages 14-17) have been fully considered, but they are not found persuasive.

Applicants argue that even one of ordinary skill in the art may find it "obvious to try" the combination of Sosnowski et al. and Muzykantov et al., one does not have a reasonable expectation of success to carry out the presently claimed invention. Applicants argue that Sosnowski et al. do not provide an enabling disclosure on using tissue-specific promoter to reduce transgene expression in non-target cells. This is

because Sosnowski et al. only provide data and examples on adenoviral vectors carrying different targeting components, and that Sosnowski et al. do not present any data on using a tissue-specific promoter to reduce transgene expression in non-target cells. The need for actual experimentation on the use of tissue-specific promoter is highlighted by the prior art that teaches unsatisfactory level of expression as a drawback for tissue-specific promoter, and absent of any data that demonstrate the feasibility of using tissue-specific promoter to obtain a desired effect, Sosnowski et al. do not provide a person having ordinary skill artisan in the art with a requisite expectation of successfully using tissue-specific promoter to reduce transgene expression in non-target cells as claimed here.

Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, Sosnowski et al. (WO 98/40508) disclose the same invention as Sosnowski et al. (U.S. Patent 6,613,563) which has claims drawn to a tropism-modified adenoviral vector system that specifically targets cells expressing a preselected receptor, wherein the adenoviral vector contains a tissue-specific promoter operatively linked to a nucleic acid molecule that encodes a gene product, and wherein the gene product enhances cellular proliferation or cellular differentiation (see claims 1-7 of the issue U.S. Patent). This indicates clearly that the teachings of Sosnowski et al. (WO 98/40508) are enabled with respect to the use of tissue-specific promoter for transgene expression in specific target cells, and thus little or no transgene expression in non-target cells.

Secondly, with respect to Applicants' argument that the prior art teaches unsatisfactory level of expression as a drawback for the use of tissue-specific promoter, the Examiner notes that the drawback concerns with the general low and insufficient expression level of tissue-specific promoter to yield therapeutic effects. Please see the teachings of Sato et al. (Biochem. Biophys. Res. Commun. 244:455-462, 1998) cited in the enablement rejection above. Nothing in the prior art indicates nor suggests the non-predictability or non-enabled use of any tissue-specific promoter to reduce transgene expression in non-target cells. On the contrary, the teachings of Sosnowski et al. (WO 98/40508) and Sosnowski et al. (U.S. Patent 6,613,563) indicate otherwise.

Thirdly, Examiner would like to note that the above rejection is made under U.S.C. 103, and therefore Sosnowski et al. (WO 98/40508) does not have to teach every element of the instant claims.

Accordingly, amended claims 1 and 3-6 stand rejected under 35 U.S.C. 103(a) for the reasons already set forth above.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER